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# Request for grant of a patent

The Patent Office
Cardiff Road
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03 FEB 2004

1. Your reference
1908701/AM

2. Patent Application Number
0402327.1

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

**Sphere Medical Limited**
**Harston Mill**
**Harston**
**Cambridgeshire**
**CB2 5GG**

Patents ADP number *(if known)* 8606295001

If the applicant is a corporate body, give the country/state of its incorporation
Country: **England**
State:

4. Title of the invention

**Method for detection of ischaemia modified albumin**

5. Name of agent
"Address for Service" in the United Kingdom to which all correspondence should be sent

**Beresford & Co**
**16 High Holborn**
**London WC1V 6BX**

Patents ADP number 1826001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications filed in the last 12 months.

| Country | Priority application number | Date of filing |
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7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute.

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8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?

**Yes**

9. Enter the number of sheets for any of the following items you are filing with this form.

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| Continuation sheets of this form | |
| Description | **4** |
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| Priority documents | |
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| Request for Substantive Examination *(Patents Form 10/77)* | |
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11. I/We request the grant of a patent on the basis of this application

Signature Beresford & Co — Date 3 February 2004

BERESFORD & Co

12. Name and daytime telephone number of person to contact in the United Kingdom

**MACDOUGALL; Alan John Shaw**

Tel: 020 7831 2290

# Patent disclosure

## Method for detection of ischaemia modified albumin

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### Introduction

Acute myocardial infarction (AMI) is a condition caused by blockage of the blood vessels supplying the heart muscle. The resulting lack of oxygen can cause permanent damage to the heart muscle (infarction) leading to illness and in many cases death. The effects of AMI can be limited or prevented by rapid treatment.

While many techniques exist to determine whether a patient has suffered from AMI, these tend to have a low degree of specificity with a number of consequences. Firstly there are a number of false negative diagnoses (failure to detect) which can result in potentially preventable subsequent injury or death, which leads to a significant cost of litigation. Health services are therefore reluctant to discharge suspected AMI patients until a large battery of tests has been carried out over a few days which in itself is a cost burden. Moreover, the cardiac markers that are routinely used to detect AMI are released during necrosis of the heart muscle and are as such a retrospective indication that damage has already occurred to the heart tissue rather than a way to detect the ischaemic event itself.

An emerging marker for the early detection of AMI is ischaemia modified albumin (IMA). Human serum albumin (albumin) is a significant component of whole blood (~40g per litre) and plays an important role in the transport of lipids and the regulation of osmotic pressure. It has been observed that a specific binding site on the albumin is altered by ischaemia, modifying the ability for albumin to bind metal ions at this site. This has lead to the Albumin Cobalt Binding (ACB®) test being developed to measure the concentration of IMA in blood for early detection of an ischaemic event, and there is a growing body of evidence that this is an effective test for the rapid detection of AMI.

The ACB® test involves determining the overall albumin concentration in a blood sample, adding a sufficient amount of cobalt ions to bind to the albumin and then colorimetrically determining the quantity of unbound cobalt to infer a concentration of IMA. Variants have been described to this approach, including use of other metal ions or fluorescent markers that bind to the unmodified albumin, and the measurement is made in an equivalent way. All require substantial sample preparation and are as such a test to be carried out in an analytical laboratory environment.

It is evident that a method to either directly measure the IMA, or to make the two measurements by which the IMA concentration is inferred in a differential manner is preferable for a number of reasons.

Firstly, direct measurement of the specific target inherently generates less error than measuring the difference between two large concentrations (albumin concentration, cobalt concentration).

Secondly, such methods can more easily be configured into a Point-of-Care (PoC) instrument to be used by front line clinical staff rather than skilled laboratory personnel. Speed of results is critical in the successful treatment of patients and a PoC instrument removes the time associated with transferring a sample to the laboratory and the results back to the clinical staff.

Thirdly, such methods may be compatible with use for repeated measurements in an arterial or venous line attached to the patient. Patients are likely to have such an access and generally require a number of measurements to be made over hours or days. An on-line on-demand system has a number of benefits including very rapid turnaround time for tests, lowering of infection risk to both patient and care giver and conservation of blood volume.

**Invention**

The concept for the invention is a method to measure IMA concentration in a patient's biological sample such as blood, plasma, serum, saliva, interstitial or other fluid, which may optionally be purified to remove, for example, red blood cells, platelets etc.

The sensor may be integrated into a patient connected device, for example an arterial or venous line as an on-line on-demand system whereby blood is periodically withdrawn over the sensor to make a measurement, or sampling of cerebrospinal fluid from a cranial drain. Other patient connected sampling systems include microdialysis probes and microneedles. Alternatively, the sensor may be incorporated into an in-vitro analyser instrument, configured to be used once or a number of times.

In one preferred embodiment the method uses a sensor to measure IMA directly. The sensor consists of a receptor material grafted onto or associated with a suitable transducer. The receptor material that has specifically been configured to respond preferentially to IMA, for example an IMA sensitive molecularly imprinted polymer. Any transduction method may be employed including electrochemical (including potentiometric, amperometric and conductimetric), optical, thermal, chromatographic, or gravimetric to name but a few.

In a second embodiment, a sample of the fluid to be analysed is mixed with a known quantity of transition metal ions in excess of the total concentration of albumin in the sample. The metal ion is preferably selected from the Groups 1b-7b or 8 of the periodic table, including the group V, As, Co, Sb, Cr, Mo, Mn, Ba, Zn, Ni, Hg, Cd, Fe, Pb, Au and Ag. The sample is left for sufficient time for unmodified albumin to react with the metal ions. A sensor is used to determine the residual concentration of unbound metal ions. The sensor consists of a receptor material and a transducer. The unbound metal ions bind to, or in some other way interact with, the receptor material to

cause a change in the receptor material. The receptor material may be a molecularly imprinted polymer or other synthetic or natural receptor. A number of material properties and transduction methods may be used including but not limited to:

- An ion sensitive membrane deposited onto an ISFET, which has inherent advantages over other ion sensitive electrodes due to the inherently improved signal to noise ratio of the technology. The membrane may be, for example, porphyrin ionophore contained within a PVC matrix to detect $Co^{2+}$ ions, as shown in Figure 1.

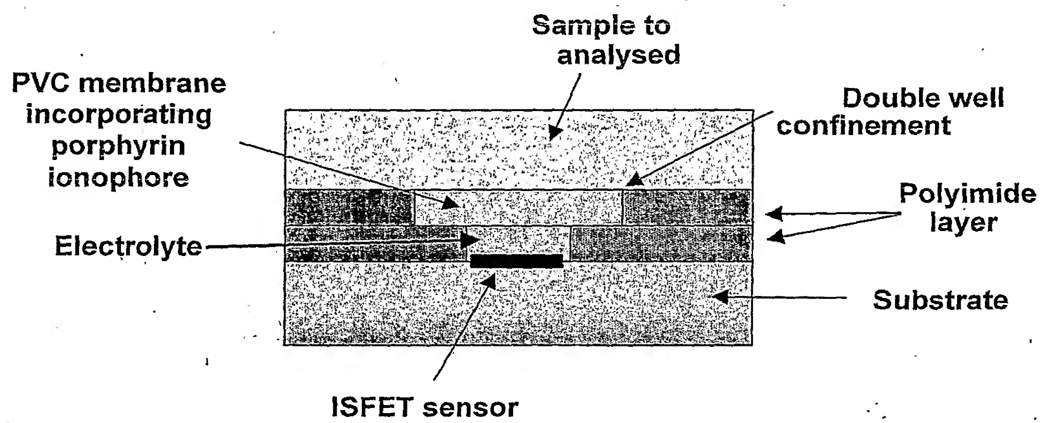


Figure 1: Schematic representation of an example of one embodiment of the invention where a sensor comprises a metal ion selective membrane deposited onto an ISFET structure. In this case a PVC membrane incorporating porphyrin is used to measure $Co^{2+}$ concentration.

- Conductivity measurements using two or four electrode transducers. Direct current and alternating current conductivity measurements may be used, including the effect of the target molecule on the conductivity response at different frequencies.
- Optical measurements on the material to monitor, for example, the change of intensity of absorption at a certain frequency, a change in fluorescence intensity or a shift in peak absorption or fluorescence intensity.

As a variant on either embodiment, the sensor may contain two or more sensitive elements, where the difference, ratio or some other function of the signals from the sensors is used to determine the IMA concentration. The sensors may be discrete components or may be combined on a single substrate, for example the chemical sensor array chip shown in Figure 2.

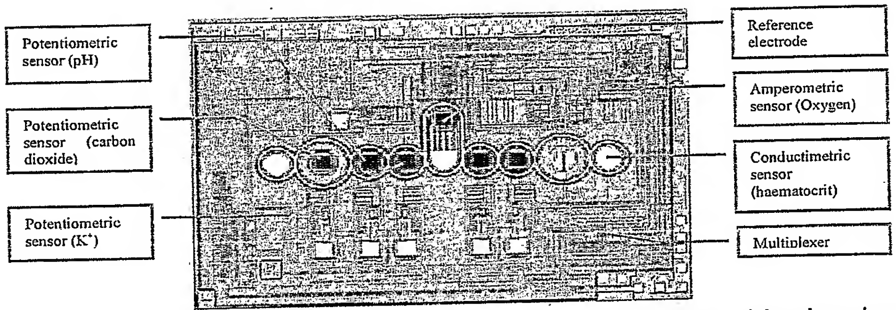


Figure 2: Example of a multi-parameter chemical sensor chip developed by Sphere Medical Ltd.

Possible combinations of sensor include:

- Sensors for IMA and for total albumin.
- Sensors for IMA and for one or more interfering species.
- Sensors for total albumin and for residual metal ions for the second embodiment described above.
- Any combinations or permutations of the above.

The method may incorporate a sensor capability for just for IMA, or preferably a panel of analytes including, for example, cardiac troponin markers.